A HEALTHY DIET TO REDUCE THE RISK OF DEMENTIA IN PEOPLE WITH A LEARNING DISABILITY

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An increased prevalence of dementia in people with a learning disability has been reported in the literature (Kerr, 2007: Dodd et al, 2015) with this being significantly increased in those with Down's syndrome. In addition people with Down's Syndrome are at an increased risk of developing dementia at an early age and are more likely to have serious adverse side effects from the leading pharmaceutical interventions such as Memantine (Hanney et al, 2012). Thus it is important to consider modifiable life style choices that reduce risk of dementia at an early stage in an individual's life, changes later in life may still have some beneficial effect though this is likely to be less significant for the individual. One modifiable life style factor that has gained epidemiological support from a vast array of studies is dietary interventions. Therefore the aim of this article is to review the evidence available on specific dietary interventions for people with a learning disability who may go on to develop a dementia. In order to support families, carers and professionals to use current evidence on nutrition that can improve the long term health of individuals with a learning disability.

Prevalence studies in people with a learning disability have estimated that rates of dementia are around 13% in people aged over 50 and 22% in those over 65, with this rising up to 77% in those over 60 who have Down's Syndrome (Kerr, 2007; Head et al, 2012). In comparison to 5-7% of those aged over 65 in the general population (Fiest et al, 2016; Prince et al, 2013). Head et al (2012) state that the degenerative process found in people with Down's Syndrome starts early with indicators of intracellular beta-amyloid and increased reactive oxygen species and oxidative stress being detected around 16 years of age. This is clinically significant given that this neurological pattern typically leads to extracellular beta-amyloid plaques which contribute to the dementia pathology. Thus dietary interventions such as anti-oxidants, polyphenols and omega-3 fish oils that are anti-inflammatory and reduce oxidative stress are advocated for in the literature in addition to the homocysteine lowering B-vitamins (Rayman et al, 2015).

Fish and Omega 3 polyunsaturated fatty acids.

Individuals with a learning disability including Down's Syndrome are low-frequency consumers of fish and omega-3 supplements and consume more pre-prepared meals which are higher in omega-6 and saturated fatty acids. This has been reflected in reduced long chain omega-3 in erythrocyte cells of people with Down's Syndrome (Nordstrom et al, 2015).

Many large epidemiological studies indicate an association with fatty acid ratio's and dementia while others fail to find such an association, as supported by the NIH state of the science Conference panel (2010) and Cochrane reviews who concluded that there is insufficient evidence to recommend omega 3 to prevent Alzheimer's disease or dementia (Dacks et al, 2013). This divergence in results has been explained by the earlier findings of Morris et al (2003) who concluded that the omega-3 fatty acid docosahexaenoic acid (DHA) but not eicosapentaenoic acids (EPA) found in fish oils positively correlated with Alzheimer's disease. Therefore studies need to assess individual fatty acids present in blood samples rather than total fatty acid compositions. More recently Cunnane et al (2012) found that DHA did not significantly differ across 3 brain cortical regions of individuals with Alzheimer's disease, mild cognitive impairment (MCI) or no cognitive impairment, while plasma DHA, n-6 fatty acids and oleic acid were lower in those with Alzheimer's disease. They postulate that analyses of lower DHA will be missed if total lipids are analysed instead of individual plasma lipids. Therefore it is suggested that for those supporting individuals with a learning disability consideration

should be given on how to increase consumption of fatty fish that is high in DHA and use of olive oil for oleic acid.

DHA and Arachadonic Acid are the most abundant fatty acids in the brain (making up 50% of brain fatty acids) which are incorporated into the cell membrane (Denis et al, 2013; Luchtman and Song, 2013). The scientific explanation of fish oils comes from evidence that fish oils enable improved membrane fluidity, intracellular signalling, neurogenesis (the birth of new nerve cells) as well as preserve synaptic function /synaptogenesis. DHA and EPA are also believed to indirectly influence brain pathology through protection from inflammation which reduces amlyoid plaque aggregation, neuroprotectin D1 which protects against cellular oxidative damage in the brain (Corsinovi et al, 2011), and through binding to peroxisome proliferator activated receptors (Dacks et al, 2013; Sydenham et al, 2012; Itua et al, 2010). In contrast omega 6 is pro-inflammatory increasing inflammatory mediators such as cyclo-oxygenases (Loef and Walach, 2013). Research has shown that these changes occur in the "frontal cortex, nucleus accumbens and the striatum, but also the hippocampus" (Luchtman and Song, 2013). Evidence has mainly come from animal studies for example decreased neurogenesis in the hippocampus of rats given omega 3 supplements and an increase in long term potentiation in glutamatergic synaptic efficacy in the hippocampus of rats that is associated with learning and memory. EPA has anti-oxidative properties that restored the electrophysiological properties of some neuronal circuits and memory in animal studies, while DHA enables protection of the glutaminegic synapse through enabling good gap junction coupling within astrocytes that maintain homeostasis (Denis et al, 2013). Criticism of mechanistic explanations come from researchers who argue that omega 3 indirectly effects cognitive functioning through improving cardiovascular and metabolic dysfunctions alongside vitamins (D,B and E found in fish) and antioxidants effecting brain atrophy on neuroimaging studies (Tan et al,2012).

Denis et al (2013) argued that omega 3 polyunsaturated fatty acids (PUFA's) slowed cognitive decline among older people without dementia from the general population and thus concurred that PUFA's have a role in reducing risk of the onset of dementia. However, fish oils may have reduced efficacy as a primary or secondary treatment for those already diagnosed with dementia. In vitro and animal models have found that DHA can change gene expression and reduce expression of inflammatory cytokines (de Urquiza et al, 2000; Vedin et al, 2012) which reduces risk of developing a dementia. Thus polyunsaturated fatty acids found in fish oils such as DHA are likely to be preventative rather than curative and thus ingestion of fatty fish at least once or twice a week should be encouraged early in life and this eating pattern maintained through to later life to delay onset of the neurodegenerative profile leading to dementia.

Due to the interactive nature of nutrients in oily fish which provides an increased amount of vitamins (especially D, B, E and A), amino acids, selenium and other minerals (Lluis et al, 2013) the beneficial effects of consuming fish are above and beyond supplementation with fish or cod liver oil capsules. In addition increasing evidence is pointing towards trans-fats and omega 3/6 ratios as being significant considerations as shown in the research by Loef and Walach (2013) and Milte et al (2011), thus advocating for replacing meals that are high in trans-fats such as burgers, take-aways and fried foods. The implications for practice is to promote a healthy diet including two servings a week of fatty fish such as salmon, mackerel or tuna when meal planning for service users with a learning disability.

B-vitamins.

A deficiency in vitamin B12 effects up to 40% of sick or institutionalised people (Andres et al, 2004) which is known to lead to neurological disorders including cognitive impairment. This can be explained physiologically by high doses of homocysteine or deficits in B12 and B9 promoting amyloid and tau protein accumulation and neuronal apoptosis (Gillette-Guyonnet et al, 2013). Thus it has been recommended that people showing cognitive decline have serum cobalamin levels analysed (Health Quality Ontario, 2013). Therefore, diet as a modifiable risk factor provides an important avenue in which to reduce this bio-psychosocial burden in those with an existing learning disability.

In the general population homocysteine has consistently been reported to correlate to Alzheimer's disease in non-diabetic samples (Morris, 2012), with raised homocysteine concentrations increasing phosphorylated tau which causes neurofibrillary tangles which are a pre-requisite of Alzheimer's like dementia (Coppede, 2010). B-vitamins have also been shown to reduce beta amyloid proteins which are believed to contribute to Alzheimer's disease (Flicker et al, 2008) and their active forms are needed for DNA replication, histone methylation, neurogenesis, neural membrane formation and proliferation and erythrocyte synthesis (see de Jager et al, 2012 and Cacciapuoti, 2013 for reviews). Additional mechanisms proposed revolve around reducing oxidative stress, optimising utilization of omega 3 fatty acids (van Wijk et al, 2012) and reducing cardiovascular disease which is associated with hyperhomocysteinemia (Ham et al, 2014).

Results from epidemiological studies support the contention that B-vitamins reduce MCI and progression of the earlier stages of dementia including Alzheimer's disease, potentially through lowering homocysteine. This relationship appears to be strongest for folate with efficacious results on various cognitive domains being reported (Morris, 2012). Further support comes from studies on brain atrophy using MRI brain scans with greatest impact of B-vitamins being shown by insufficiency in B12 and low holo-transcobalamin (Vogiatzoglou et al, 2008). Epidemiological studies are unable to show directional causality and evidence exists that age and neurocognitive decline effects malnutrition and consequently B-vitamin intake (von Arnim et al, 2013), thus causality may be bi-directional.

Randomised controlled trials have thus been warranted which have shown inconsistent results. Meta-analysis and sub-analysis of randomised controlled trials have highlighted that efficacy of treatment may be dependent on baseline characteristics including B-vitamins being within the sub-optimal range and biomarkers such as homocysteine levels being above the threshold of 11.5µmol/L (Jerrneren et al, 2015; Smith et al, 2010). In addition combined treatment with folate B6 and B12 is more effective than single B-vitamins, with synergy with other nutrients such as poly-unsaturated fatty acids also increasing their efficacy (Jerrneren et al, 2015; Scheltens et al, 2012). Concurrently homocysteine levels decrease further with combined B-vitamin treatment compared to single preparations offering further support to this mechanistic theory (Vogel et al, 2009).

B-vitamin trials have been more effective in MCI and reducing speed of progression to dementia than in clinically diagnosed dementia cases, with 82% of known dementia cases being non-reversible (Djukic et al, 2015) and thus it is difficult to achieve either clinical or significant results in this cohort. More specific measures of dementia such as brain atrophy have shown some improvement following a course of B-vitamins particularly in posterior brain areas that are associated with dementia such as

the bilateral hippocampus, lingual and fusiform gyrus that are involved in visuo-spatial learning and memories with atrophy also noted in the cerebellum which is required for working and autobiographical memory (Douaud et al, 2013; Jerneren et al, 2015). This appears on further analysis to be related to vitamin B12 though further studies are required to corroborate this finding (Douaud et al, 2013). Thus B-vitamins may make subtle differences in those with MCI and those already diagnosed with dementia which are enhanced by duration of treatment. It is therefore important to encourage children with a learning disability to eat dark green leafy vegetables, yeast extract, milk and foods high in B12 and folate which they can continue to consume through adulthood to older ages.

Recently Prasher and Prasher (2016) have published their findings from a study on serum folate and B12 levels in individuals with Down's Syndrome concluding that no significant association was found between these nutrients and Alzheimer's disease. Critique of these findings are based on the small sample size (66 adults with Down's Syndrome and dementia compared to 37 individuals with Down's Syndrome not diagnosed with Alzheimers Disease). The authors of this paper highlight this as a possible reason for the heterogeneity with studies conducted in the general population. Further criticism comes from the mean age of the sample and controls being 56 years, due to beta-amyloid plaques developing in their 30's or earlier, it could be postulated that some participants in the control group had the early stages of dementia which the diagnostic criteria failed to recognise given the atypical presentation often found in people with Down's Syndrome.

Although none of the researchers from studies cited above have reported adverse effects from B-vitamin supplementation caution should be taken when recommending B-vitamins without awareness of current nutrient status due to the finding of Moore et al (2014) and Malouf et al (2008). These researchers showed that B-vitamin supplementation may be detrimental to cognition in those that have optimal levels of B12 prior to supplementation. An additional warning comes from evidence that folic acid supplementation can mask B12 deficiency leading to neurological damage (Morris et al, 2007). A recent systematic analysis by Otaegui-Arrazola et al (2014) concluded that studies giving a low dose of B-vitamins are more likely to have positive results on cognitive decline than those giving supra-pharmacological doses. No adverse effects have been reported from encouraging individuals to consume foods that are high in the B-vitamins making this a viable option for individuals with a learning disability with unknown serum levels. The additional benefit of a healthy diet incorporating a range of B-vitamins comes from evidence that these nutrients work in synergy with omega-3 fatty acids and that a nutrient rich diet will also provide a range of vitamins, minerals, anti-oxidants and polyphenols that can work in conjunction to improve health outcomes.

Anti-oxidants and polyphenols.

Anti-oxidants such as vitamin C and vitamin E as well as minerals including selenium have been proposed as important for a brain protective diet to reduce risk of neuro-degeneration (Rayman et al, 2015). Plant food sources are also rich in other chemical compounds that limit damage caused by pathogens and radiation from sunlight (UVB) these substances that can be metabolised and used as anti-oxidants by the body are known as polyphenols. Anti-oxidants and polyphenols can be found in a variety of food sources such as fruit, vegetables and nuts. These highly nutritious foods provide sources of polyphenols such as anthocyanins found in berries and red skinned fruits, hesperidin

found in citrus foods, tocopherols found in pistachio nuts, phenylethanoid found in olive oil and flavonols in dark chocolate.

In the general population research into the mechanistic actions of polyphenols impact on the brain has been conducted. One polyphenol that has received a lot of interest is anthocyanins which are found in red fruit and berries. These have been found to reduce oxidative stress, inflammation and viral infections in addition to their anti-proliferative properties (Subash et al, 2014). Blueberries and strawberries have also been found to enhance dopamine and thus intracellular communication within the brain and reverse declines in β-adrenergic receptor function (Bickford et al, 2000; Balk et al, 2006), that inhibit the formation of and destabilise β-amyloid fibrils, reduce ratios of Aβ40/42, improve brain glutathione and ascorbate levels, and inhibit COX 1 and 2 expression which are key pathogenic features due to increased Reactive Oxygen Species (ROS) in neurodegenerative diseases such as dementia (Vepsäläinen et al, 2013; Subash et al, 2014).

Anthocyanin aglycons such as cyaniding-3-0-β-D-glucopyranoside have also been found to reduce cerebral ischemic damage through reduction of ROS, as shown by significantly reduced infarct volume and increased cell viability following oxygen glucose deprivation in vitro and in vivo (Kang et al, 2006; Sweeney et al, 2002). Finally evidence is also emerging that berries may provide benefit for multiple sclerosis patients (Xin et al, 2012).

Studies on dietary intakes of people with a learning disability have reported an increase in snacking between meals as well as an increased consumption of bread, cakes, meat products and milk and reduced consumption of fruit and vegetables compared to the general population (Adolfsson et al 2008). This is corroborated by recommended daily intakes and biochemical markers of micro-nutrients not meeting the recommended amounts (Hoey et al 2016). Thus it could be postulated that people with a learning disability consume less antioxidants and polyphenols which has the potential to increase reactive oxygen species and pathological damage.

Studies in people with Down's Syndrome have only investigated 3 polyphenol compounds including Epigallocatechin-3-gallate found in green tea, resveratrol found in red grapes and Hydroxytyrosol from olive oil. These have all significantly reduced oxidative stress or regulated mitochondrial stress reducing impaired neurogenesis as well as suppressing neuroinflammation which are hallmarks of the neuro degenerative disorders (Vacca et al, 2016). Further studies are now needed to investigate the effects of other antioxidants such as anthocyanins, hesperidin, tocopherols and flavonols in people with Down's Syndrome.

Conclusion.

A varied diet that is rich in fruit, vegetables, nuts, olive oil, milk and the occasional piece of dark chocolate can serve as protective of developing a dementia. With evidence that encouraging a healthy and varied diet early in life and sustaining this through adulthood and later in life promotes neurological health. The biopsychosocial benefits of reducing the double burden of developing degenerative diseases in people with a learning disability is an important consideration for any healthcare professional given the increased prevalence rates of dementia found in people with a learning disability.

Implications for practice.

Encourage people with a learning disability to eat fatty fish such as salmon, mackerel or tuna twice a week.

Encourage snacks of fruit or vegetables crudités. Citrus fruit, peppers, plums, grapes and berries are particularly good as they are high in antioxidants such as vitamin C as well as polyphenols.

Ground or whole nuts such as pistachios and brazil nuts that are high in selenium can be added to breakfast cereal to increase antioxidant intake.

Ensure that good sources of vitamin B12 and folate are provided, which can be found in dark green leafy vegetables, milk, yeast extract, unprocessed red meat.

Multi-disciplinary team involvement from dieticians, General Practitioners and Learning Disability Nurses can offer valuable support and guidance in meeting nutrient requirements of individuals in accordance to their specific needs and preferences.

General Practitioners can also organise for serum levels of B-vitamins and other nutrients to be checked to ensure that deficiencies are not left untreated.

Remember the earlier in life individuals with a learning disability start to eat healthy the better, but it's never too late.

References.

Adolfsson P, Sydner Y, Fjellström C, Lewin B, Andersson A. (2008). Observed dietary intake in adults with intellectual disability living in the community. Food and Nutrition Research. 2008;52.

Andrès E, Loukili N, Noel E, Kaltenbach G, Abdelgheni M, Perrin A, Noblet-Dick M, Maloisel F, Schlienger J, Blicklé J. (2004). Vitamin B12 (cobalamin) deficiency in elderly patients. Canadian Medical Association Journal 2004 Aug 3;171(3):251-9.

Balk E, Chung M, Raman G, Tatsioni A, Chew P, Ip S, DeVine D, Lau J. (2006). B vitamins and berries and age-related neurodegenerative disorders. Evidence Report Technology Assessment (Full Rep). 2006 Apr;(134):1-161.

Bickford P, Gould T, Briederick L, Chadman K, Pollock A, Young D, Shukitt-Hale B, Joseph J. (2000). Antioxidant-rich diets improve cerebellar physiology and motor learning in aged rats. Brain Research. 2000 Jun 2;866(1-2):211-7.

Cacciapuoti F.(2013). Lowering homocysteine levels with folic acid and B-vitamins do not reduce early atherosclerosis, but could interfere with cognitive decline and Alzheimer's disease. Journal of Thrombosis and Thrombolysis. 2013 Oct;36(3):258-62.

Coppede, F. (2010). One-Carbon Metabolism and Alzheimer's Disease: Focus on Epigenetics. Current Genomics. 2010 Jun; 11(4): 246–260.

Corsinovi L, Biasi F, Poli G, Leonarduzzi G, Isaia G. (2011). Dietary lipids and their oxidized products in Alzheimer's disease. Mol Nutr Food Res. 2011 Sep;55 Suppl 2:S161-72.

Cunnane S, Schneider J, Tangney C, Tremblay-Mercier J, Fortier M, Bennett D, Morris M. (2012). Plasma and brain fatty acid profiles in mild cognitive impairment and Alzheimer's disease. Journal of Alzheimers Disease. 2012;29(3):691-7.

Dacks P, Shineman D, Fillit H. (2013). Current evidence for the clinical use of long-chain polyunsaturated n-3 fatty acids to prevent age-related cognitive decline and Alzheimer's disease. Journal of Nutrition and Healthy Aging. 2013 Mar;17(3):240-51.

de Jager C. (2012). Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. International Journal of Geriatric Psychiatry. 2012 Jun;27(6):592-600.

Denis I, Potier B, Vancassel S, Heberden C, Lavialle M. (2013) Omega-3 fatty acids and brain resistance to ageing and stress: body of evidence and possible mechanisms. Ageing Res Rev. 2013 Mar;12(2):579-94.

de Urquiza A, Liu S, Sjoberg M, Zetterstrom R, Griffiths W, et al. (2000). As cited in Vedin et al (2012).

Djukic M, Wedekind D, Franz A, Gremke M, Nau R. (2015). Frequency of dementia syndromes with a potentially treatable cause in geriatric in-patients: analysis of a 1-year interval. European Archives of Psychiatry and Clinical Neuroscience. 2015 Aug;265(5):429-38.

Dodd, K. Coles, S. Finnamore, T. Holland, T. Gangadharan, S. Sheepers, M. Strydom, A. Whitwham, S. and Wilson, S. (2015). Dementia and people with intellectual disabilities: Guidance on the assessment, diagnosis, interventions and support of people with intellectual disabilities who develop dementia. British Psychological Society : Leicester.

Douaud,G., Refsum,H., de Jager,C., Jacoby,R., Nichols,T., Smith,S., and Smith, D. (2013). Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. Proceedings of the Nationall Academy of Science U S A. 2013 Jun 4; 110(23): 9523–9528.

Flicker L, Martins R, Thomas J, Acres J, Taddei K, Vasikaran S, Norman P, Jamrozik K, Almeida O. (2008). B-vitamins reduce plasma levels of beta amyloid. Neurobiology of Aging. 2008 Feb;29(2):303-5. Epub 2006 Nov 20.

Fiest K, Jetté N, Roberts J, Maxwell C, Smith E, Black S, Blaikie L, Cohen A, Day L, Holroyd-Leduc J, Kirk A, Pearson D, Pringsheim T, Venegas-Torres A, Hogan D. (2016). The Prevalence and Incidence of Dementia: a Systematic Review and Meta-analysis. Canadian Journal of Neurological Sciences. 2016 Apr;43 Suppl 1:S3-S50.

Gillette-Guyonnet S, Secher M, Vellas B. (2013). Nutrition and neurodegeneration: epidemiological evidence and challenges for future research. British Journal of Clinical Pharmacology. 2013 Mar;75(3):738-55.

Ham A, Enneman A, van Dijk S, Oliai Araghi S, Swart K, Sohl E, van Wijngaarden J, van der Zwaluw N, Brouwer-Brolsma E, Dhonukshe-Rutten R, van Schoor N, van der Cammen T, Zillikens M, de Jonge R, Lips P, de Groot L, van Meurs J, Uitterlinden A, Witkamp R, Stricker B, van der Velde N. (2014). Associations between medication use and homocysteine levels in an older population, and potential mediation by vitamin B12 and folate: data from the B-PROOF Study. Drugs and Aging. 2014 Aug;31(8):611-21.

Hanney M, Prasher V, Williams N, Jones E, Aarsland D, Corbett A, Lawrence D, Yu L, Tyrer S, Francis P, Johnson T, Bullock R, Ballard C; on behalf of the MEADOWS trial researchers (2012). Memantine for dementia in adults older than 40 years with Down's syndrome (MEADOWS): a randomised, double-blind, placebo-controlled trial. Lancet. 2012;379:528-536.

Head, E. Powell, D. Gold, B. and Schmitt, F. (2012). Alzheimer's Disease in Down Syndrome. European Journal of Neurodegenerative Disease. 2012 Dec; 1(3): 353–364.

Health Quality Ontario. (2013). Vitamin B12 and cognitive function: an evidence-based analysis. Ontario Health Technology Assessment Series. 2013;13(23):1-45. Review.

Hoey E, Staines A, Walsh D, Corby D, Bowers K, Belton S, Meegan S, McVeigh T, McKeon M, Trépel D, Griffin P, Sweeney M. (2016). An examination of the nutritional intake and anthropometric status of individuals with intellectual disabilities: Results from the SOPHIE study. Journal of Intellectual Disabilities. 2016 Jul 11.

Itua I, Naderali E. (2010). Review: omega-3 and memory function: to eat or not to eat. American Journal of Alzheimers Disease and Other Dementia. 2010 Sep;25(6):479-82.

Jernerén F, Elshorbagy A, Oulhaj A, Smith SM, Refsum H, Smith A. (2015). Brain atrophy in cognitively impaired elderly: the importance of long-chain ω-3 fatty acids and B vitamin status in a randomized controlled trial. American Journal of Clinical Nutrition. 2015 Jul;102(1):215-21.

Kang T, Hur J, Kim H, Ryu J, Kim S. (2006). Neuroprotective effects of the cyanidin-3-O-beta-d-glucopyranoside isolated from mulberry fruit against cerebral ischemia. Neuroscience Letters. 2006 Jan 2;391(3):122-6. Epub 2005 Sep 19.

Kerr, D (2007) Understanding Learning Disability and Dementia: Developing Effective Interventions. London: Jessica Kingsley Publishers

Lluís L, Taltavull N, Muñoz-Cortés M, Sánchez-Martos V, Romeu M, Giralt M, Molinar-Toribio E, Torres J, Pérez-Jiménez J, Pazos M, Méndez L, Gallardo J, Medina I, Nogués M. (2013). Protective effect of the omega-3 polyunsaturated fatty acids: Eicosapentaenoic acid/Docosahexaenoic acid 1:1 ratio on cardiovascular disease risk markers in rats. Lipids in Health Disease. 2013 Oct 1;12:140

Loef M and Walach H. (2013). The omega-6/omega-3 ratio and dementia or cognitive decline: a systematic review on human studies and biological evidence. Journal of Nutritional in Gerontology and Geriatrics. 2013;32(1):1-23.

Luchtman D, Song C. (2013). Cognitive enhancement by omega-3 fatty acids from child-hood to old age: findings from animal and clinical studies. Neuropharmacology. 2013 Jan;64:550-65.

Malouf M, Grimley E, Areosa S. (2008). Folic acid with or without vitamin B12 for cognition and dementia. Cochrane Database Systematic Review. 2008 Oct 8;(4):CD004514.

Milte C, Sinn N, Street S, Buckley J, Coates A, Howe P. (2011). Erythrocyte polyunsaturated fatty acid status, memory, cognition and mood in older adults with mild cognitive impairment and healthy controls. Prostaglandins Leukotrienes and Essential Fatty Acids. 2011 May-Jun;84(5-6):153-61.

Moore E, Ames D, Mander A, Carne R, Brodaty H, Woodward M, Boundy K, Ellis K, Bush A, Faux N, Martins R, Masters C, Rowe C, Szoeke C, Watters D. (2014). Among vitamin B12 deficient older people, high folate levels are associated with worse cognitive function: combined data from three cohorts. Journal of Alzheimers Disease. 2014;39(3):661-8.

Morris M, Evans D, Bienias J, Tangney C, Bennett D, Wilson R, Aggarwal N, Schneider J. (2003). Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol. 2003 Jul;60(7):940-6.

Morris M. (2012). Nutritional determinants of cognitive aging and dementia. Proceedings in of the Nutrition Society. 2012 Feb;71(1):1-13.

Morris M. (2012b). The role of B vitamins in preventing and treating cognitive impairment and decline. Advances in Nutrition. 2012 Nov 1;3(6):801-12.

Morris M, Jacques P, Rosenberg I, Selhub J. (2007). Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. American Journal of Clinical Nutrition. 2007 Jan;85(1):193-200.

NIH state of the science Conference panel (2010). Accessed at http://consensus.nih.gov/2010/alzstatement.htm#speakers on the 21.12.2016.

Nordstrøm M, Paus B, Andersen L, Kolset S. (2015). Dietary aspects related to health and obesity in Williams syndrome, Down syndrome, and Prader-Willi syndrome. Food and Nutrition Research. 2015 Feb 3;59:25487.

Otaegui-Arrazola A, Amiano P, Elbusto A, Urdaneta E, Martínez-Lage P. (2014). Diet, cognition, and Alzheimer's disease: food for thought. European Journal of Nutrition. 2014 Feb;53(1):1-23.

Prasher, V. and Prasher, M. (2016). Folate, vitamin B(12), Down syndrome and Alzheimer's disease. International Journal of Geriatric Psychiatry Volume 31, Issue 12, Version of Record online: 28 OCT 2016.

Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri C. (2013). The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers and Dementia. 2013 Jan;9(1):63-75.

Rayman, M. Ridland, V. Sharpe, K. and Westcott, P. (2015). "Healthy Eating to reduce the risk of dementia". Kyle books: London.

Scheltens P, Twisk J, Blesa R, Scarpini E, von Arnim C, Bongers A, Harrison J, Swinkels S, Stam C, de Waal H, Wurtman R, Wieggers R, Vellas B, Kamphuis P. (2012). Efficacy of Souvenaid in mild

Alzheimer's disease: results from a randomized, controlled trial. Journal of Alzheimers Disease. 2012;31(1):225-36.

Smith A, Smith S, de Jager C, Whitbread P, Johnston C, Agacinski G, Oulhaj A, Bradley K, Jacoby R, Refsum H. (2010). Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. PLoS One. 2010 Sep 8;5(9):e12244.

Subash S, Essa M, Al-Adawi S, Memon M, Manivasagam T, Akbar M. (2014). Neuroprotective effects of berry fruits on neurodegenerative diseases. Neural Regeneration Research. 2014 Aug 15;9(16):1557-66.

Sweeney M, Kalt W, MacKinnon S, Ashby J, Gottschall-Pass K. (2002). Feeding rats diets enriched in lowbush blueberries for six weeks decreases ischemia-induced brain damage. Nutrition and Neuroscience. 2002 Dec;5(6):427-31.

Sydenham E, Dangour A, Lim W. (2012). Omega 3 fatty acid for the prevention of cognitive decline and dementia. Cochrane Database Systematic Review. 2012 Jun 13;6.

Tan Z, Harris W, Beiser A, Au R, Himali J, Debette S, Pikula A, Decarli C, Wolf P, Vasan R, Robins S, Seshadri S. (2012). Red blood cell ω-3 fatty acid levels and markers of accelerated brain aging. Neurology. 2012 Feb 28;78(9):658-64.

Vacca, R. Valenti, D. Caccamese, S. Daglia, M. Braidy, N. Nabavi, S. (2016). Plant polyphenols as natural drugs for the management of Down syndrome and related disorders. Neuroscience and Biobehavioral Reviews, December 2016, Vol.71, pp.865-877.

von Arnim C, Dismar S, Ott-Renzer C, Noeth N, Ludolph A, Biesalski H. (2013). Micronutrients supplementation and nutritional status in cognitively impaired elderly persons: a two-month open label pilot study. Nutrition Journal. 2013 Nov 15;12(1):148.

van Wijk N, Watkins C, Hageman R, Sijben J, Kamphuis P, Wurtman R, Broersen L.(2012). Combined dietary folate, vitamin B-12, and vitamin B-6 intake influences plasma docosahexaenoic acid concentration in rats. Nutrition and Metabolism (London). 2012 May 30;9(1):49.

Vedin I, Cederholm T, Freund-Levi Y, Basun H, Garlind A, Irving G, Eriksdotter-Jönhagen M, Wahlund L, Dahlman I, Palmblad J. (2012). Effects of DHA-rich n-3 fatty acid supplementation on gene expression in blood mononuclear leukocytes: the OmegAD study. PLoS One. 2012;7(4)

Vepsäläinen S, Koivisto H, Pekkarinen E, Mäkinen P, Dobson G, McDougall G, Stewart D, Haapasalo A, Karjalainen R, Tanila H, Hiltunen M. (2013). Anthocyanin-enriched bilberry and blackcurrant extracts modulate amyloid precursor protein processing and alleviate behavioral abnormalities in the APP/PS1 mouse model of Alzheimer's disease. Journal of Nutrition and Biochemistry. 2013 Jan;24(1):360-70.

Vogel T, Dali-Youcef N, Kaltenbach G, Andrès E. (2009). Homocysteine, vitamin B12, folate and cognitive functions: a systematic and critical review of the literature. International Journal of Clinical Practrice. 2009 Jul;63(7):1061-7.

Vogiatzoglou A, Refsum H, Johnston C, Smith S, Bradley K, de Jager C, Budge M, Smith A. (2008). Vitamin B12 status and rate of brain volume loss in community-dwelling elderly. Neurology. 2008 Sep 9;71(11):826-32.

Xin J, Feinstein D, Hejna M, Lorens S, McGuire S. (2012). Beneficial effects of blueberries in experimental autoimmune encephalomyelitis. Journal of Agricultural Food Chemistry. 2012 Jun 13;60(23):5743-8.